SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MICROBIOLOGY DEVICES PANEL MEETING

MEDICAL DEVICES ADVISORY COMMITTEE

September 7, 2023
9:00 a.m. EST

Attendees

Chairperson

Barbara Van Der Pol, PhD, MPH
Professor of Medicine and Public Health
Division of Infectious Diseases
University of Alabama - Birmingham, AL

Voting Members

Ricardo M. La Hoz, MD, FACP, FAST, FIDSA
Director of Solid Transplant Infectious Diseases
Associate Professor of Medicine
Division of Infectious Diseases
University of Texas Southwestern Medical Center - Dallas, TX

Thomas A. Moore, MD, FACP, FIDSA
Clinical Professor of Medicine
Infectious Disease Physician
University of Kansas School of Medicine - Wichita, KS

Temporary Non-Voting Members

Cathy A. Petti, MD
Clinical Microbiologist
President and CEO
Health Spring Global, Inc. - Carson City, NV

Emily A. Blumberg, MD, FACP, FIDSA, FAST
Professor of Medicine
Director of Transplant Infections Diseases Department of Medicine
Infectious Disease Fellowship Program
University of Pennsylvania School of Medicine - Philadelphia, PA

Camille N. Kotton, MD, FIDSA, FAST
Clinical Director of Transplants and
Immunocompromised Host Infectious Diseases
Massachusetts General Hospital
Associate Professor at Harvard Medical School - Boston, MA

Angela M. Caliendo, MD, PhD, FIDSA, FAAM
Warren Alpert Foundation Professor
Executive Vice Chair of Medicine
Alpert Medical School of Brown University - Providence, RI

Marcus R. Pereira, MD, MPH
Associate Professor of Medicine
Medical Director of the Transplant Disease Program
Director of Clinical Services, Division of Infectious Diseases
Columbia University Medical Center - New York, NY

Valerie L. Ng, MD, PhD
Professor Emeritus of the Department of Laboratory Medicine
Laboratory Director, Laboratory Medicine and Pathology
Director, Transfusion Services
Lab Director and Chair of the Department of Alameda Health System
University of California, San Francisco - Alameda, CA

Nicolas A.H. Wentzensen, MD
Senior Investigator and Deputy Director of the
Clinical Genetics Branch at the National Cancer Institute
Head, Clinical Epidemiology Unit
Division of Cancer Epidemiology and Genetics - Bethesda, MD

Kathleen G. Beavis, MD
Professor of Pathology
University of Chicago - Chicago, IL

Gary W. Procop, MD
CEO American Board of Pathology
Professor of Pathology
Cleveland Clinic Lerner College of Medicine - Cleveland, OH

Charles Y. Chiu, MD, PhD
Professor in Laboratory Medicine and Infectious Diseases
University of California - San Francisco, CA

Industry Representative

Bradford M. Spring, MS
Head of Global Regulatory Policy and Intelligence at
Roche Diagnostics - Washington, DC

Consumer Representative

Roblena E. Walker, PhD
CEO of EMAGAHA, Inc.
Research Scientist - Mableton, GA

Patient Representative

Jennifer A. Schwartzott, MS - North Tonawanda, NY

FDA Participants

Timothy Stenzel, MD, PhD
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CDRH/OPEQ/OHTVII/DMD, FDA - Silver Spring, MD

Uwe Scherf, M.Sc., PhD
Division Director
CDRH/OPEQ/OHTVII/DMD, FDA - Silver Spring, MD

Kristian Roth, PhD
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Press Contact

James McKinney

Designated Federal Officer

Candace Nalls,
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FDA Presenters

Scott McFarland, J.D.
Regulatory Counsel Immediate Office
CDRH/OPEQ, FDA - Silver Spring, MD

Maria Ines Garcia, PhD
Branch Chief for General Viral and Hepatitis
OHT7/CDRH/OPEQ, FDA - Silver Spring, MD

Ryan Karsner, MD
Deputy Branch Chief for General Viral and Hepatitis
OHT7/CDRH, FDA - Silver Spring, MD

Noel Gerald, PhD
Branch Chief for Bacterial Respiratory and Medical Countermeasures
OHT7/CDRH, FDA - Silver Spring, MD

Open Public Hearing Speakers

Yasmin Ibrahim, MD, PhD
Public Health Program Director, Hepatitis B Foundation
Doylestown, PA

Sue Wong, DO
Internist, Director for the Viral Hepatitis Programs and the
Center for Asian Health
Cooperman Barnabas Medical Center in New Jersey
Senior Advisor of Global Health to the Hepatitis B Foundation

Diana Zuckerman, MD
President of the National Center for Health Research

Robert Gish, MD
Medical Director of Hepatitis B Foundation
Medical Director of Asian Pacific Health Foundation - San Diego, CA

CALL TO ORDER & INTRODUCTIONS

Dr. Van Der Pol, the Panel's chairperson, called the meeting to order, advised that the panel members participating in today's meeting have received training in FDA device law and regulations, and announced the agenda for the meeting: to provide preliminary input on the potential future reclassification of nucleic acid and serology based in vitro diagnostic devices indicated for use to aid in the diagnosis of hepatitis B virus, HBV, infection and/or for the use to aid in the management of HBV infected patients; serology based in vitro diagnostic devices indicated for use to aid in the detection of past, recent, or current infection with human parvovirus B19; and cell mediated immune reactivity in vitro diagnostic devices indicated for use to aid in identification of in vitro responses to peptide antigens that are associated with mycobacterium tuberculosis infection and/or for the use as detection of effector T-cells that respond to stimulation by M tuberculosis agents from Class III to Class II.

Dr. Van Der Pol reminded the public and panelists that this is a non-voting meeting and asked committee members and the FDA attending virtually to introduce themselves.

CONFLICT OF INTEREST STATEMENT & APPOINTMENT OF NON-VOTING MEMBERS

Upon completion of introductions, **Candace Nalls,** the Designated Federal Officer, read the conflict of interest statement and made general announcements, noting that based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict of interest waivers have been issued. With the exception of the industry representative, **Bradford M. Spring,** all members or consultants of the panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest law and regulations. **Candace Nalls** reminded all members and

consultants that if the discussions involve any other products of firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, that participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

Candace Nalls advised that for the duration of the Microbiology Devices Panel meeting on September 7, 2023, **Dr. Roblena Walker** and **Ms. Jennifer Schwartzott** have been appointed to serve as temporary non-voting members. **Dr. Walker** serves as consumer representative to the Antimicrobial Drugs Advisory Committee at CDER. **Ms. Schwartzott** serves as patient representative consultant to the Cellular Tissue and Gene Therapies Advisory Committee at CBER. These individuals are special government employees who have undergone the customary conflict of interest review. **Candace Nalls** made general announcements to the panel regarding identifying themselves before speaking to help aid the transcriber and announced **James McKinney** as the press contact for today's meeting.

The meeting was handed back to **Dr. Van Der Pol**, and she invited FDA participant **Dr. Timothy Stenzel** to give some opening remarks. **Dr. Timothy Stenzel** welcomed the panel and expressed appreciation for their participation and attention to the important topics that will be discussed. **Dr. Van Der Pol** invited the FDA to start their first presentation.

SESSION ONE - FDA PRESENTATION
OVERVIEW OF DEVICE REGULATION AND HBV ASSAYS

Dr. Scott McFarland provided a high-level overview of the medical device classification process. He explained the three classes of medical devices: Class I, Class II, and Class III. Devices are classified based on the controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls, Class II are subject to both general and special controls, and Class III are subject to general controls and pre-market approval. He noted that importantly, a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Most Class I devices do not require FDA pre-market review prior to being marketed. A few examples of Class I devices include elastic bandages, handheld manual cervical instruments, and different culture mediums. There's also an alternative pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they're not life sustaining, life supporting, or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury. And these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance, safety, and effectiveness.

General controls are basic requirements to apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include ensuring the devices are not misbranded or adulterated, following good manufacturing practices, meeting establishment, registration, and device listing requirements, and adhering to reporting and record keeping requirements. Class II devices are those devices which cannot be classified into Class I because

general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls provide such assurance.

Class III devices are those which cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and the devices are life sustaining or life supporting or are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval through a premarket approval application, PMA, prior to being marketed. Examples of Class III devices include breast implants and IVDs for the detection and differentiation of human papillomaviruses.

A flowchart was presented that walks the general decision-making process for each of the classes that were discussed. **Dr. McFarland** advised they start by determining whether general controls are sufficient to provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class I. If not, they ask whether there is sufficient information that allows them to be able to develop special controls that, in combination with the general controls, provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class II. If not, then it would be Class III if the device is life supporting or life sustaining or if it is of substantial importance in preventing impairment of human health or if it presents a potential unreasonable risk of illness or injury. If the device is not life supporting or life sustaining or of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury, they end up back at a Class I designation.

Dr. McFarland again reiterated what was being asked of the panel. He advised that the input should include an identification of the risk to health presented by each device type and a discussion of whether each device is life supporting, life sustaining, of substantial importance of preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. The panel will also be asked to discuss whether sufficient information exists to develop special controls, and what those special controls should be, that, in combination with the general controls, would provide reasonable assurance of safety and effectiveness for each device type. Then the FDA will consider the available evidence, which includes the input received from this panel and the public and consider potential future reclassification of the device types discussed today.

Dr. Ines Garcia presented on the potential hepatitis B virus, HBV, device reclassification. HBV represents a substantial public health burden. CDC estimates that chronic HBV infection in the US affects between 580,000 to 1.17 million people. Because HBV infection can be asymptomatic, many individuals are unaware of their HBV infectious status. Approximately 95 percent of adults with acute HBV infection recover completely, whereas five percent of adults develop chronic HBV. Infants born to women who are hepatitis B surface antigen positive are at high risk of HBV infection. In the absence of treatment, infants infected with HBV have a 90 percent risk of progression to chronic HBV, and up to 25 percent of infants who acquire chronic HBV infection will die prematurely. Chronic HBV increases the risks of

liver damage, liver cancer, and liver failure. Therefore, it is important for adults to be screened, as well as pregnant people during pregnancy.

Dr. Garcia presented a table showing the different interpretations and the follow-up actions to take based on the results of HBV antigen and antibody tests. HBV antigen assays have the intended use where the assay may be used to screen for hepatitis B in pregnant women who are at risk for acquiring hepatitis B during the perinatal period. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection, the state of infection or associated disease not determined in persons with signs and symptoms, and in persons at risk for hepatitis B infection.

Qualitative antibody assays have the intended use where the assay may be used as an aid in the diagnosis of adults with acute or chronic hepatitis B infection and in the determination of the clinical status of HBV infection individuals in conjunction with other HBV serological markers for the laboratory diagnosis of HBV Disease association with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis. Quantitative surface antigen antibody assays have the intended use where the assay may be used as an aid in the determination of susceptibility to HBV infection for individuals prior to or following HBV vaccination or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis, in whom etiology is unknown. The detection of anti-HBS is indicative of laboratory diagnosis of seroconversion from HBV infection or from vaccination.

The risk to health for HBV antibody and antigen tests include false negative and false positive results, both of which may result in misdiagnosis, incorrect HBV infected status determination, including delay, failure to perform additional diagnostic procedures, and linkage to appropriate care, unnecessary testing in pursuit of another potential cause, and potential transmission of HBV to others, missed opportunity for vaccination, and psychological stress to the patient. A way to minimize potential sources of false negatives and/or false positives is for the assay to have optimal sensitivity.

When a patient is diagnosed with the antibody and antigen assays, they are then tested with HBV DNA to guide treatment decisions. Because HBV treatments are lifelong, patients receive regular HBV DNA testing. The goal of HBV treatment is sustained suppression of HBV replication, also known as undetectable HBV DNA, which leads to improved liver enzymes, loss of HBeAg, with or without the detection of HBeAg antibodies, and improvement in liver histology. HBV molecular assays have the following intended use where the assay may be used as an aid in the management of patients with chronic HBV infection undergoing antiviral therapy. The assay can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment. The results from the assay must be interpreted within the context of all relevant clinical and laboratory findings.

The risk to health for HBV molecular tests include false negatives, falsely decreased results, incorrect interpretation of test results, failing to correctly operate the test, and/or false

positives, falsely elevated results, incorrect interpretation of test results, failing to correctly operate the test, both of which may result in withholding or premature discontinuation of HBV antivirals, potential transmission of HBV to others, potential for other unassisted necessary medical procedures to investigate other causes of liver disease, administration or continuation of unnecessary antiviral treatment, or psychological stress to the patient.. A way to minimize potential sources of false negatives and/or false positives is for the assay to have optimal sensitivity. specificity. Special controls could potentially be developed to mitigate the risks of false positive, false negative, incorrect results interpretation, and failure to correctly operate the device. The goal is to maintain consistently high performance across devices with similar intended uses and for individual devices of the total product lifecycle.

In conclusion, **Dr. Garcia** read the four questions for the panel to discuss.

OPEN PUBLIC HEARING

Ms. Nalls read the open public hearing disclosure process statement. **Dr. Van Der Pol** advised that FDA received four requests for the open public hearing portion and each speaker was given 5 minutes to speak.

Dr. Ibrahim from Pennsylvania spoke about the chronic burden of hepatitis B and some of the populations or groups it affects that have less access to care or needed resources. She spoke about barriers and cost of testing. She requested the FDA to reclassify from Class III to Class II.

Dr. Wong spoke about the burden of hepatitis B and advised that down classifying would be instrumental to increasing access to testing, which would be one of the biggest hurdles to clear in the goal of eliminating hepatitis B.

Dr. Zuckerman stated that although she is not familiar with the assays in question, in speaking with other experts she feels lowering the standards from Class III to Class II could be harmful to patients. She asked the panel to carefully consider if lowering the classification is in the best interest of patients.

Dr. Robert Gish believes down-classifying would bring more testing options which would be beneficial and important to patients, including helping with stigma and discrimination, and would, ultimately, aid in the goal of eliminating hepatitis B.

SESSION ONE PANEL DELIBERATIONS
QUESTION ONE

Dr. Van Der Pol read the first question: One, please comment on whether you believe FDA has identified a complete and accurate list of risks to health presented by the following devices: Qualitative HBV antigen tests, qualitative HBV antibody tests, quantitative anti-HBS tests, and/or quantitative HBV molecular tests. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risks should be included in the overall risk assessment of the devices listed above.

Dr. Valerie Ng advised that she would like to add testing performed as point of care as a risk. **Dr. Wentzensen** believes the list is good but could be expanded. **Dr. Van Der Pol** advised one thing not on the list is the list of benefits, and risk benefit ratio is also an important consideration. **Ms. Schwartzott** wondered what the percentages of false negative and false positives are in Class III testing assays and if anyone knew what those same percentages were in Class II similar tests already on the market.

Dr. Garcia stated for current Class III products, sensitivity is about 98% and specificity is 99%. **Dr. Scherf** emphasized that down-classification does not imply they are expecting a difference in performance. **Dr. Pereira** clarified that he is interpreting that changing from Class III to Class II, there is no minimum standard but also no difference in expectations or requirements.

Dr. Stenzel responded that when they write special controls for a device that is down classified, they can put those performance expectations into those special controls. **Dr. Scherf also** confirmed this point. **Dr. Stenzel** explained what special controls are in case anyone didn't know. **Dr. Van Der Pol** asked again about the list of risks. **Dr. Pereira** would like to see the mention of false positive or negative surface antibody results leading to either unnecessary vaccination or not vaccinating someone.

Dr. Blumberg advised to add that leaving them as Class III may limit access to those tests. **Dr. La Hoz's** opinion is that the pros will be larger than the cons. **Dr. Caliendo** believes keeping it as Class III would reduce access to care and feels that is a risk. **Dr. Van Der Pol** said it may also be a benefit, depending on how you look at things, but it was decided it should be added to the list of risks. **Dr. Kotton** was in favor of downgrading.

Dr. Van Der Pol summarized that panel generally believes the risk are inclusive and exhaustive. Some risks need to be quantified. Risks may be use case dependent. While risks are comprehensive, they may need to be restructured to provide more detail. Given the information of current Class II tests, risks have been, in part, addressed by having high quality assays.

QUESTION TWO

Dr. Van Der Pol read question two: Please discuss potential mitigation measures/controls that FDA should consider that could mitigate each of the identified risks.

Dr. Van Der Pol advised this is the point at which we should discuss the mitigation measures and controls, and so mitigation measures can be describing what populations it's appropriate to use these or what clinical context it's appropriate to use these. Controls can also include setting a minimum sensitivity or minimum specificity that the assay would have to hit. So it's not related to Class III that they have to have high sensitivity specificity. Class II assays can be required to have the same performance levels.

Dr. Kotton mentioned an issue of hepatitis B surface antigen positivity within one to two weeks after receiving a vaccine, so this should be addressed in package insert or consumer based

education. **Dr. Procop** advised it would be great to open with "lower performance standards will not be accepted." **Dr. Beavis** suggested specifying that a single serologic assay alone should not be used as the sole basis for instituting therapy. There was lots of discussion of making sure performance characteristics shouldn't change. **Dr. Caliendo** agreed with a suggestion by **Dr. Petti** to say, "used in conjunction with."

Dr. Chiu brought up the point that there is a difference between qualitative and quantitative assays. This is really a panel of four different assays. He said there is certainly risk with quantitative assays of inappropriate use. It's more of a challenge regarding standardization because these are quantitative assays. **Dr. Karsner** with FDA clarified that intended use statements for all of these assays are as an aid in the diagnosis of hepatitis B, and they have language in the labeling that results should be interpreted in context of clinical picture and other test results. **Dr. Stenzel** reiterated that the standards don't have to change for the down-classification. The standards can remain the same.

After very robust discussion, **Dr. Van Der Pol** summarized the panel believes that there are mitigations that should be put in place. Mitigations include labeling about when it's appropriate to us, intended use mitigations that cover what clinics or what circumstances testing is being done, maybe disentangling diagnostics from screening, requiring follow-up testing or confirmatory testing, and labeling must include language such as an aid in diagnosing. Special controls, including sensitivity and specificity, should either remain where they are, or there need to be carefully considered special controls there. The qualitative and quantitative assays may actually have different needs in their labeling and mitigations.

QUESTION THREE

Dr. Van Der Pol read question three: Based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls.

Dr. Blumberg is in favor of reclassification. She mentioned concerns about providing adequate guidance for interpretations, specifically to guide treatment. **Dr. Procop, Dr. La Hoz, Dr. Caliendo, Dr. Beavis, Ms. Schwartzott, Dr. Pereira, Mr. Spring, Dr. Petti, Dr. Wentzensen, Dr. Kotton, Dr. Walker, Dr. Chiu, Dr. Moore, Dr. Ng** were all in favor of reclassification.

Dr. Van Der Pol summarized panel believes it would be appropriate, based on amount of data they have about how these tests perform, to consider starting the downgrade process. The panel is not concerned, but is adamant that special controls do need to be in place that dictate the high level of sensitivity and specificity and that special controls will need to be in place to mitigate any potential risks of using these in certain patient populations and to distinguish perhaps between diagnostics and screening, and that, for quantitative assays, there are special controls that cover limited detection, limited quantification, and linearity so that it's knowns exactly what these results mean.

QUESTION FOUR

Dr. Van Der Pol read question four: Currently there are no FDA authorized tests for the detection and quantitation of hepatitis B surface antigen. Please discuss appropriate intended use for such a device, potential risks associated with that intended use, and whether mitigation measures/special controls could be developed that, in addition to general controls, mitigate risks to health.

Dr. Ng advised quantification for her would not be with a surface antigen, it would be with a NAT test. She would like to know the relationship of an antigen test to a NAT. **Dr. Moore** agreed with **Dr. Ng** that surface antigen to him is not useful clinically. **Dr. Caliendo** suggested maybe an inexpensive alternative to a NAT. The majority of input advised there was not enough information to know how this would be utilized or where it would be adopted.

Dr. Van Der Pol summarized with regard to question four, the panel doesn't feel like there's sufficient information to help develop special controls. So at this time, there is not enough information to support moving this to Class II. So if someone does present data to the FDA about a test such as this, it should be evaluated under a Class III mechanism, according to the information is available at this time.

SESSION TWO - FDA PRESENTATION
PARVOVIRUS B19

Dr. Karsner discussed potential reclassification of qualitative serology based Parvovirus B19 antibody in vitro diagnostic devices from Class III to Class II with special controls. FDA is ultimately seeking recommendations from the panel members and the public on whether sufficient information exists such that the development of special controls, which along with general controls, could mitigate the risks from these devices such that the devices would provide a reasonable assurance of safety and effectiveness and, therefore, can be eligible for a Class II designation.

The intended uses for these Parvovirus antibody assays are for the detection of IgM antibodies and IgG antibodies as evidence of Parvovirus B19 infection and may be used as an aid in the diagnosis of past or current infection with Parvovirus B19. The tests are labeled such that a clinician should consider the results of these assays as presumptive for risk of fetal infection with Parvovirus. The test may be used as an aid in the diagnosis of fifth disease or erythema infectiosum.

Regarding the public health burden, most individuals are infected in childhood, resulting in 50 to 80 percent IgG seroprevalence reported in serosurveys. However, much of the public health burden largely rests with a few specific populations. Chronic or reactivated infection can be associated with increased morbidity for high-risk populations, such as immunocompromised patients or those with hemolytic anemia. The virus can also spread through blood, and, therefore, a pregnant person is at risk of passing the virus to the fetus causing serious complications due to severe anemia, such as hydrops fetalis, and miscarriage or intrauterine fetal death.

Risks to health are associated with failure of the diagnostic device to perform as intended or errors in the use of the diagnostic device or other reasons for false results and subsequently improper patient management. A false non-reactive result may cause spreading of the virus to other individuals through contact, and thus present a public health risk. Parvovirus B19 infection is generally self-limiting and benign for most healthy individuals, but, again, may pose a more grave threat of chronic or reactivated infection with associated morbidity for high-risk populations such as immunocompromised patients or those with hemolytic anemia, as discussed. The virus can also spread through blood. So, again, therefore, a pregnant person with Parvovirus infection with a false negative result is at risk of passing the virus to the fetus without the knowledge of the patient or the health care provider. This can cause serious complications such as hydrops fetalis, and miscarriage or intrauterine fetal death.

If Parvovirus antibody assays are reclassified as Class II, special controls would be written to mitigate the risks. The goal would be to maintain consistent high performance across devices with similar intended uses and for individual devices over the total product's life cycle. There are some specific considerations for Parvovirus antibody devices and their validation. Specifically, there are very few Parvovirus antibody tests currently on the market, which may lead to difficulty formulating a composite comparator during the clinical validation of a new Parvovirus test. Prevalence of Parvovirus IgM, even in the intended use population, can lead to difficulty in enrollment of IgM positive individuals in clinical and analytical studies. Confidence intervals around performance point estimates can, therefore, be quite wide; and, therefore, there can be some uncertainty about the performance of the tests, even in otherwise well-designed and/or enriched studies.

There are, of course, additional concerns related to cross-reactivity and interfering substances, along with other similar considerations for any other antibody tests. Regarding the additional considerations for the potential reclassification itself, manufacturers would no longer be regulated under the Class III paradigm, but instead under the Class II paradigm, which has fewer regulatory requirements. Considering the probable health benefits of the use of these devices and the nature and known incidents of the risks of the devices, FDA on its own initiative is contemplating reclassifying these post amendments Class III devices into Class II.

FDA believes that when used as indicated, Parvovirus antibody tests can provide significant benefits to clinicians and patients, including making a serological determination of past, recent, or current infection with Parvovirus B19 as an aid in the diagnosis of fifth disease or erythema infectiosum, and presumptive risk of fetal infection with Parvovirus B19. FDA's reasons for reclassification are based on the scientific and medical information available regarding the nature, complexity, and risks associated with Parvovirus antibody assays. The safety and effectiveness of this device type has become established since the initial approval of the first Parvovirus antibody assays in 1997. **Dr. Karsner** read the questions for panel at the conclusion of his presentation.

SESSION TWO PANEL DELIBERATIONS
QUESTION ONE

Dr. Van Der Pol advised that there were no requests to speak during the open public hearing session. She asked if the panel had clarifying questions from the FDA before beginning deliberations. Since there were none, they went straight into deliberations regarding question one.

Dr. Van Der Pol read question one: Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by Parvovirus antibody assays. Please comment on whether you disagree with any of these identified risks or whether you believe any other risks should be included in the overall risk assessment of Parvovirus antibody assays.

Dr. Van Der Pol asked if the panel has everything they would like to see discussed as a potential risk. Are there any risks that were described that you think are not appropriate for Parvovirus antibody testing? **Dr. Moore** asked the reason for this coming up for discussion. **Dr. Van Der Pol** reminded him that part of the FDA's charge is to have all tests classified at the lowest classification appropriate, and she asked the panel if there is enough data to move it from Class III to Class II with appropriate controls.

Dr. Stenzel chimed in that FDA underwent a review of all Class III devices in microbiology and looked at those they felt should be considered for down-classification. They previously underwent reviews to down-classify from Class II to Class I. This is an ongoing process to make sure that, when appropriate, they look at the possibility of down-classification. **Dr. Pereira** said there will likely be similar discussion with Parvovirus as related to prior hepatitis B. He doesn't often use this test in his practice but has a sense that there is significant rate of false positive results, particularly in regard to IgG, and false negative results with IgM. He asked if anyone on the panel could provide more data on the performance of these tests.

Dr. Karsner advised the performance tended to be over 96%. For some tests such as IgM for acute infection in certain populations was about 91%, but it depends on the comparator being used and how clinical truth is established. In general, positive percent agreement with comparator was between 97 and 99%. And per FDA tracking databases to track errors, there were not a significant number of tests having reported false results to the FDA.

Dr. Blumberg wondered how much of an access issue there is with this test. **Dr. Procop** shared some of the same concerns **Dr. Pereira** raised and advised it likely depends on use case. He believes use of the test during pregnancy is where special controls might be particularly applicable to how the test is used. **Dr. La Hoz** and **Dr. Petti** shared the concerns of **Dr. Procop and Dr. Pereira. Dr. Caliendo** feels FDA has outlined appropriate risks. She found it interesting that almost everybody mentioned PCR for Parvovirus, and there's not even a test available. So a mitigating measure may be for the FDA to help companies get a quantitative cargo PCR out there because that's the test many are using clinically.

Dr. Van Der Pol summarized the panel in general feels like the risks described by the FDA are appropriate, and that they've captured all of those risks. The concerns that were raised by the panel were whether or not those risks would perhaps also need to include special controls for special populations and getting back to intended use, especially for use in pregnant women. There need to be risks that maybe are associated with ordering appropriately, especially as it

relates to IgG versus IgM, because those have very different interpretive values, and potentially that the risks of false negative and false positives apply as well to other Parvovirus types of testing, which would include molecular tests for DNA.

QUESTION TWO

Dr. Van Der Pol read question two: Please discuss potential mitigation measures/controls that FDA should consider that could mitigate each of the identified risks.

Dr. Van Der Pol stated they already talked about appropriate labeling to clarify intended use and when it's appropriate to order the different tests in different populations and how to interpret the results. She asked if anyone has anything other than labeling and intended use statements and making sure that sensitivity and specificity are set at appropriate levels.
Dr. La Hoz spoke about transplant recipients often receive IVIG as treatment for rejection or donor specific antibodies, and advised it's challenging to interpret serological assays in patients that have received these types of products. He didn't know if that really applied. **Dr. Van Der Pol** believes it applies in regards to one of the mitigations being reflexing to a molecular test, as opposed to making a treatment decision based on antibody test alone.

Dr. Ng, Dr. Caliendo, and **Dr. Van Der Pol** discussed whether you can list that as a mitigation when there isn't a molecular test available that's gone through FDA process.
Dr. Van Der Pol advised that this is just throwing out ideas and possibilities. Just because it's been discussed doesn't mean it will be one of the controls. **Dr. Karsner** clarified that for a lot of serology tests that FDA regulates, labeling includes limitations about caution in interpreting serology tests in immunocompromised individuals, which has a lot to do with etimology of immunocompromised can be different depending on who the person is, what's going on, what medications they are taking, etc. And then he spoke about the challenges with establishing a viral load for Parvovirus.

Dr. Van Der Pol summarized the panel agrees special controls are needed, and they need to be population specific. And they need to include labeling, and they need to include appropriate sensitivity and specificity performance measures, especially understanding specificity of IgG, as well as sensitivity of IgM, because that's going to perhaps be used more often during pregnancy. But all immunocompromised patients need to have appropriate safety measures, warning labels, and limitations to interpreting these results. The panel didn't have specific concerns about what those labels or limitations should look like.

QUESTION THREE

Dr. Van Der Pol read question three: Based on the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls.

Dr. Van Der Pol called on the panel members and then summarized that there is a true consensus here. No concerns to share. Everybody is supportive of the fact that there are sufficient data to help develop special controls and labeling, etc., and the panel strongly recommends that the agency consider down-classifying Parvovirus antibody tests.

SESSION THREE - FDA PRESENTATION
M TUBERCULOSIS INTERFERON GAMMA RELEASE ASSAYS

Dr. Noel Gerald talked about potential M. tuberculosis interferon gamma release assays device reclassification. The purpose of this meeting is to discuss the potential future reclassification of mycobacterium tuberculosis, referred to as TB, cell mediated immune reactivity in vitro diagnostic devices such as interferon gamma release assays, referred to as IGRAS. FDA is seeking recommendations from the panel members and the public on whether sufficient information exists such that the development of special controls, which along with general controls, can mitigate the risks from these devices, such that the devices would provide a reasonable assurance of safety and effectiveness and, therefore, can be eligible for a Class II designation.

He discussed the public health burden. Pulmonary tuberculosis is the most common clinical presentation of tuberculosis in adults, and infection occurs by transmission of the organism through inhaling airborne particles that contain MTB that are released from individuals with active pulmonary disease. Most people who are infected with TB are asymptomatic, which is known as latent TB infection, and the latent infections are not contagious and do not result in clinical disease in most cases. But, overall, there's a five to ten percent lifetime risk for patients with latent infection to develop active TB disease. And this risk varies to many factors, including immunosuppression. Of the United States TB cases, more than 80 percent are attributed to reactivation of untreated latent TB. There are numerous antibiotic regimens available to treat TB. However, adverse drug reactions are common, and patients should be closely monitored while on therapy.

IGRAs are indirect tests for TB. They're in vitro blood tests which measure T-cell release of interferon gamma following stimulation with TB antigens to aid in the diagnosis of TB. The commonly used ESAT-6 and CFP-10 IGRA peptide antigens are specific to organisms in the Mycobacterium tuberculosis complex, but they're absent from the BCG strains that are used in vaccines and most non-tuberculous mycobacteria. The IGRAs are useful in BCG vaccinated persons and in clinical scenarios where a single patient visit is advantageous. In contrast the tuberculin skin test, TST, is another type of indirect test for TB which requires a second patient visit 48 to 72 hours after administration. Additionally, it is known that prior BCG vaccination or infection with non-tuberculosis mycobacteria can cause a reaction in the TST.

But these are the risks to health of inaccurate results that we've identified: False negative results, incorrectly operating a device causing false negative results, and incorrectly interpreting results as negative. Results can lead to progression of active or reactivation of latent TB disease in individuals, spread of disease in the community, or missed opportunities for diagnosing an underlying condition or disease such as HIV infection that may have been unrecognized and may

be contributing to the progression to active TB. False positive results, incorrectly operating the device causing false positive results, and incorrectly interpreting results as positive results can lead to unnecessary treatment within the associated drug toxicities for these therapies, unnecessary patient isolation and radiologic imaging and laboratory testing, and unneeded contact tracing, resulting in wasted healthcare resources.

So aspects of IGRA device validation, labeling, and use that should be taken into consideration when thinking of potential mitigations are discussed here. Labeling includes clinical performance in several different populations, which include, patients at low risk for previous TB infection in the absence of risk factors, patients with culture confirmed or NAT confirmed active pulmonary TB infection, patients at high risk of latent TB, and patients with a history of non-tuberculous mycobacterial infection or colonization, which could be cross-reactive. The labeling includes the performance estimates. These are truly estimates in the absence of a reference standard. The specificity is estimated in comparison to the expected negative results for a population at low risk of TB infection. And sensitivity is estimated from the population with active pulmonary TB. Labeling can also include performance as additional information agreement to other indirect tests. So positive percent agreement or negative percent agreement for the results of the TST test or another IGRA.

The labeling does highlight the limitations of studies conducted in the absence of a true reference standard, and it includes other limitations that are relevant, such as a negative result does not exclude the possibility of infection within tuberculosis and noting that these tests should not be used alone. They must be used in conjunction with each individual's epidemiological history, current medical status, and the results of other diagnostic evaluations. So other things to take into consideration include the years of experience the clinicians have had at this point on recognizing the limitations of these tests and considering the appropriate uses. And then also the existence of guidelines from organizations such as the American Thoracic Society, CDC, and IDSA that explicitly discuss the appropriate use and interpretation of these tests.

Some additional considerations for reclassification. Reclassification has the potential to increase opportunities for innovative diagnostic devices in this space. There would be reduced regulatory requirements for sponsors and manufacturers. So PMA specific requirements would be removed, but the belief is that the risks can be mitigated by special controls. **Dr. Gerald** concluded by reading the questions for the panel to consider.

Q&A WITH FDA

Dr. Van Der Pol, after a 15 minute break, advised that at this point in the agenda there is space for an open public hearing, but FDA received no requests to speak during this portion of the meeting, so she continued on to Q&A with FDA regarding the presentation.

Mr. Spring asked if they have previously down-classified other tuberculosis assays to Class II. **Dr. Noel Gerald** confirmed that they reclassified molecular tests on NAT assays from Class III to Class II.

Dr. Ng asked that IGRAs are primarily used to identify latent TB, but the positive predictive agreement is based on active TB, correct? **Dr. Gerald** stated that the intended use doesn't explicitly state latent TB, but they understand that's a big part of how they are used clinically, and he advised that it's very difficult to conclusively show that someone has latent TB until it's progressed to active TB.

Dr. Chiu said it was mentioned in the presentation that down-classifying this category of assay, it might open the way for other kind of tests in that category, and he wants to know if FDA is referring to a category of potentially human host response biomarkers, or are they referring to it because it makes this test a little different than other tests that look directly for either nucleic acid or protein from the pathogen, but rather focus more on the host response? **Dr. Gerald** said they were not meaning to specifically indicate or imply biomarkers in general. It is really specifically on cell mediated immune response assays. That was the intent.

Dr. Pereira asked if there was any data on this for the quantifier on tests in terms of indeterminate results and how often those come back. **Dr. Gerald** advised that what they do know about the rate of indeterminants is that first time and what's seen in the validation studies.

QUESTION ONE

Dr. Van Der Pol read question one: Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by M. tuberculosis assays, in this case, specifically, interferon gamma release assays. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of M. tuberculosis assays. Do you think that the risks are fully described, and do you think that there are any risks that are described that don't belong that need to be removed?

Dr. Van Der Pol clarified that the risks were false negatives and false positives, either from operating the device incorrectly or just incorrectly interpreting the device, or just the device not performing as well as it might have. So do you think those risks are sufficient?
Dr. Blumberg thinks the risks as described are accurate. She voiced concerns that both **Dr. Kotton** and **Dr. La Hoz** brought up about this test being so much about population-based risk, and quantifying the risk really varies. So risk of indeterminate or inaccurate response is greater in immunosuppressed populations. It's also greater in people with active infection.
Dr. La Hoz feels the risks have been identified correctly. He also feels there are ways to mitigate by labeling and establishing standards in different populations.

Dr. Stenzel wanted everyone to know that there are two providers in the US who provide this testing category. Even though they are approved, they have more annual work to do to maintain their approvals. And then if they want to make changes or if they need to move to expand their manufacturing footprint, they need to submit that to FDA and then be inspected, which is all very difficult. Lowering the classification also is beneficial to the providers.

Dr. Van Der Pol cautioned that you would hate to see somebody drop their manufacturing because they couldn't deal with the regulatory environment. **Dr. Pereira**

mentioned in addition to indeterminate results, the only other thing he could think to add is follow-up testing, sort of repeat quantifier on tests. **Dr. Petti** stated one other risk is for false positives that require a subsequent workup, which could cause them to be delayed for their treatment of other conditions and could be associated with significant morbidity.

Dr. Kotton highlighted the point that with quantiferon testing, you get either positive, negative, or indeterminate results. With T spot, it's either positive, negative, or borderline. And the "indeterminate" tag is really problematic. When she gives lectures, many people come up and say, don't you know that indeterminate means that they should get latent TB prophylaxis? **Dr. Kotton** then explains that indeterminate just means the test didn't work. **Dr. Gerald** agreed that they have also run into this issue, this kind of vagueness of use of the terms indeterminate, equivocal, or borderline. They are trying to be more explicit when talking with sponsors going forward.

Dr. Van Der Pol summarized that in general the risks were captured. There wasn't any the panel thought should be removed from the list. However, the risks list could benefit by calling out specific populations in which those risk levels were higher, as opposed to others in which maybe it was lower, obviously, immunocompromised people, but also those people with active disease for whom the risk of a false positive might be more relevant, but also the risks in populations at low risk or low prevalence of disease where the positive predictive value might be quite low. And so the risk of a false positive. So both false positives and negatives are already described on there, but the panel felt like maybe they should be described in more specific detail for different populations.

And also one of the risks that didn't appear to be included was the risk of an indeterminate result, because that did have clinical ramifications, and people have had to deal with that in different ways. And then, finally, the risk of inappropriate use, which you specifically mentioned in the risks that are listed the risk of incorrect use, but, again, it's probably worth listing the risk of people ordering this test when this test is not appropriate for that particular patient. And one of the risks that specifically could be called out was when you have an incorrect result that could lead to treatment delays for other diseases. And so perhaps that was worth calling that risk out as well.

QUESTION TWO

Dr. Van Der Pol read question two: Please discuss potential mitigation measures or controls that FDA should consider that could mitigate each of the identified risks.

Dr. Procop is supportive of the downgrade, but all pre-analytics that are currently in place should stay in place and be held to that same high-level degree of stringency. **Dr. Van Der Pol** mentioned that maybe manufacturers should be encouraged to describe results as invalid or uninterpretable rather than equivocal because they are not interpretable for a clinician. **Dr. Kotton** explained the mitigation strategy she personally uses. **Dr. La Hoz** has a similar patient population as **Dr. Kotton** and shared some of his mitigation strategies, including a calculator that factors race factors, age, etc.

Dr. Petti suggested a labeling mitigation strategy stating that confirmation needs to be made by the same or another method. **Dr. La Hoz** stated that he doesn't feel, in either extreme, repeating the test is necessary, and **Dr. Van Der Pol** suggested wording like, without including positives or negatives, but consider re-test based on pre-test positive probabilities? **Dr. Procop** said just pre-test probabilities, because it could be either negative or positive. **Dr. Moore** mentioned that he agreed with **Dr. La Hoz** to discourage, as much as possible, re-testing and really leave that out of the discussion other than to say consider it for patients who have a high pre-test probability, wo have a negative test or indeterminate test, and then additional investigation may be worthwhile.

Dr. Van Der Pol asked if this is something the panel feels that labeling mitigation or a package insert mitigation would make it more clear to clinicians how to act based on these test results, or does the panel feel there is not enough information? Because if the panel feels there is not enough information, that would be the piece that would drive whether this can be changed from Class III to Class II.

Dr. Gerald advised that tests that are approved now do have statements to the effect about the potential for false positives and negatives, and even in the intended use statements, they really are only supposed to be used in conjunction with these other history and other test results. He stated some of the conversation happening is a little bit beyond what they would put into the individual label of a specific test. So for a manufacturer that has decided to have an indeterminate or borderline result, they could advised them that they need explicit instructions on what someone should be doing based on that result. Anything larger than that, in terms of clinical algorithm or what other things you should be going to next, that's more outside their realm and more in the larger society guidelines.

Dr. Gerald also mentioned that this is really beyond the scope of discussion today to talk about indeterminate, borderline, equivocal results. It is something FDA can have a conversation with sponsors about, but the idea is that there is a category where it is a valid result. It still provides some information. He gave the example that in these IGRAs, some percentage of the indeterminate results are because the sample was mishandled. So the person could be positive, and the sample was mishandled, and it's indeterminate. However, they can have the discussion with the sponsor, and they do suggest that they have more simple interpretations.

Dr. Wentzensen said the discussion reminds him of what they have currently in the cervical cancer prevention arena where statements were "according to clinical recommendations or guidelines, and then these guidelines developed by 20 or more clinical societies across the US because there are a lot more applications in the screening and management that could be covered in the indication. **Dr. Beavis** cautioned that we can't be looking for perfection here. **Dr. Ng** said she wanted to jump on **Dr. Beavis's** bandwagon, and then also separately made a comment that to a laboratorian, invalid and indeterminate are two very different things.

Dr. Van Der Pol agreed and mentioned that maybe uninterpretable might be better. Either way, it may be time to all sit down and thing about what language has been used historically and what language should be used going forward that clarifies things, which is beyond the scope of this meeting. **Dr. Beavis** suggested perhaps the package insert could have

explanations for what indeterminate means, whether it's specimen handling, whether it's something int he nature of the specimen itself, the patient specimen, or what are the different reasons. That could help the interpretation of that result.

Dr. Van Der Pol summarized that this was a really interesting conversation probably because it is a slightly different type of test and partly because it's an indirect test. That puts our thinking caps on a little bit differently. We talked about one of the things that I wrote down that I think, even though we didn't come back to the specific language here, I still think it comes back to there probably needs to be some sort of labeling or limitation that includes what can go wrong if the pre-analytical steps are not accurately followed. Because I do think that that is one of the reasons you do get those indeterminants or whatever word it is with that particular assay. We talked about having labeling and limitations that were sort of specific to populations, whether that be populations with active TB populations that are immunocompromised or populations that had low pre-test probability or high pre-test probability. And so that's something to think about, but I have to say that amongst the panel, we did not actually ever achieve consensus on what we thought that labeling should be, but the panel clearly identified a point that we think is a point of weakness that needs to be addressed at some point.

And I think that there were no real calls for stringency any different from the Class III level of stringency for sensitivity and specificity, but that we have enough data to understand how the assays that currently are marketed as Class III assays are working, and we think that those performance characteristics are useful clinically. And so if we have special controls that use that same sort of range of sensitivity and specificity, that will probably meet the needs of providers.

QUESTION THREE

Dr. Van Der Pol read question three: Based upon the information presented and future discussion at panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for this device from Class III to Class II, subject to special controls.

Dr. Van Der Pol explained this is essentially the panel deciding if we have opinions about whether this product and other assays, not the specific product, but this type of assay, could be reclassified from Class III to Class II based on the information we have currently about what the risks and mitigations are that could be applied to these types of assays. **Dr. Van Der Pol** asked first if anyone felt there is not enough information to reclassify these. No one responded. **Dr. Van Der Pol** called on the panel members that raised their hands, and all were in agreement with the down-classification.

Dr. Van Der Pol summarized the panel is in overwhelming agreement that these types of test should be considered for down-classification from Class III to Class II, and that there is sufficient data to take action on moving that forward.

CUSTOMER SUMMATIONS, COMMENTS, OR CLARIFICATIONS

Dr. Van Der Pol asked the consumer, industry and patient representatives if they have additional comments about any of the three topics that were discussed.

Dr. Walker, the consumer representative, stated she was in agreement with every thought and sentiment that was shared from the panel members.

Mr. Spring, the industry representative, also completely agreed with the panelists' comments and the decisions and recommendations that were made.

Patient representative, **Ms. Schwartott** stated the more options we have is better to get care to the patients.

FDA SUMMATIONS, COMMENTS, OR CLARIFICATIONS

Dr. Stenzel stated this was a highly productive, very engaging, very robust discussion today, and FDA is very grateful. He summarized that except for the hepatitis B surface antigen quantification, they have solid support, sometimes unanimous, for down-classification from Class III to Class II.

With that, **Dr. Van Der Pol** expressed thanks to the panel, the FDA, and all of the open public hearing speakers for their contributions and meeting was adjourned.

I approve the minutes of this meeting as recorded in this summary.

Barbara Van Der Pol, Ph.D., M.P.H.
Chairperson

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I certify that I attended this meeting on September 7, 2023 and that these minutes accurately reflect what transpired

Candace J. Nalls -S

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Designated Federal Officer